IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:	)	
Kevin Liu et. al.	)	GROUP ART UNIT: 1624
Application No.:10/820,647	)	EXAMINER: Rao, Deepak
FILED: 04/07/2004	)	DATE: October 27, 2008

TITLE: ARYL COMPOUNDS AS MODULATORS OF PPARS AND METHODS OF TREATING METABOLIC DISORDERS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF PURSUANT TO 37 CFR 41.37

Sir:

This brief is in furtherance of the Notice of Appeal filed on March 28, 2008. A five-month extension of time is requested. Authorization is hereby given to treat this and any future reply, requiring a petition for an extension of time under 37 CFR § 1.135 for its timely submission or payment of fee, as incorporating a petition for extension of time for the appropriate length of time or authorization to pay any required fees. Please charge any appropriate fees to Deposit Account No. 503299.

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Real party in interest.

The real party in interest is Kalypsys, Inc., the assignee of record.

Related appeals and interferences.

There are no known prior or currently pending appeals, judicial proceedings, or interferences which may be related to, directly affect or be affected by, or have a bearing on the Board's decision in the pending appeal.

Status of claims.

Claims 1-13, 18-36, 41-57, and 59-70 are currently pending. Of these, claims 50 and 70 are allowed, and claims 1-13, 18-36, 41-49, 51-57, and 59-69 are rejected.

Status of amendments.

No amendments have been entered subsequent to final rejection.

Summary of claimed subject matter.

Below is a description of each appealed claim and where support for each portion of that claim relevant to the appeal at hand can be found in the specification. Claims 50 and 70 have been found allowable. Claims 14-17, 37-40, and 58 have been canceled.

Independent claim 1 claims a compound of Formula I (pp. 3-5), or a pharmaceutically acceptable N-oxide, pharmaceutically acceptable prodrug (pp. 13, 27), pharmaceutically active metabolite (pp. 5, 27), pharmaceutically acceptable salt (pp. 26-27, 31), pharmaceutically acceptable ester (pp. 14-15, 27), pharmaceutically acceptable amide (pg. 13), or pharmaceutically acceptable solvate(19) thereof (collectively, pp. 3-5).

Claim 2 depends from Claim 1, wherein Ar_2 is selected from the group consisting of phenyl (pp. 5, 8, 43-45), naphthyl (pp. 9, 45-48), anthracene (pg. 5) , and phenanthrene (pg. 5).

Claim 3 depends from Claim 2, wherein Ar_2 is phenyl (pp. 5, 8, 43-45).

Claim 4 depends from Claim 3, having the structure shown (pp. 5, 8, 43-45).

Claim 5 depends from Claim 2, wherein Ar_2 is naphthyl (pp. 9, 45-48).

Claim 6 depends from Claim 4 or Claim 5, wherein R_1 is alkyl (pp. 5, 8, 9, 12, 38-48), optionally substituted with one or more optionally substituted carbocyclic or heterocyclic rings (collectively, pp. 5, 13-14).

Claim 7 depends from Claim 6, wherein said alkyl is a lower alkyl (pp. 5, 12, 38-44, 46-48).

Claim 8 depends from Claim 7, wherein said lower alkyl is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, and sec-butyl (pp. 5, 8, 9, 12, 38-44, 46-48).

Claim 9 depends from Claim 6, wherein said carbocyclic ring is phenyl (pp. 5, 13).

Claim 10 depends from Claim 9, wherein said phenyl is optionally substituted with one or more substituents selected from the group consisting of lower alkyl, halogen, perhaloalkyl, hydroxy, alkoxy, nitro, and amino (pp. 5, 8, 9, 43, 45).

Claim 11 depends from Claim 10, wherein said substituent is perhaloalkyl (pp. 5, 8, 9, 15, 18, 43, 45).

Claim 12 depends from Claim 11, wherein said perhaloalkyl is trifluoromethyl (pp. 5, 8, 9, 43, 45).

Claim 13 depends from Claim 1, wherein R_1 is alkyl substituted with 4-bis(trifluoromethyl)phenylmethyl (pp. 6, 43, 45) .

Claim 18 depends from any of Claim 4 and Claim 5, wherein R_2 is optionally substituted alkyl (pp. 6, 8, 9, 12, 38-48).

Claim 19 depends from Claim 18, wherein said alkyl is a lower alkyl (pp. 6, 12, 40-46).

Claim 20 depends from Claim 19, wherein said lower alkyl is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, and sec-butyl (pp. 6, 8, 9, 12, 40-46).

Claim 21 depends from Claim 20, wherein R_2 is ethyl (pp. 6, 40-46).

Claim 22 depends from Claim 1, wherein R_3 is hydrogen, halogen or optionally substituted alkyl (pp. 6, 12, 18-19).

Claim 23 depends from Claim 22, wherein said optionally substituted alkyl is an optionally substituted lower alkyl (pp. 6, 12, 18-19).

Claim 24 depends from Claim 23, wherein said optionally substituted lower alkyl is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, and sec-butyl (pp. 6, 12).

Claim 25 depends from Claim 1, wherein R_3 is methyl (pp. 6, 12).

Claim 26 depends from Claim 1, wherein R_3 is hydrogen (pg. 6).

Claim 27 depends from Claim 1, wherein B and the propyloxy substituents on Ar_2 are ortho to each other (pp. 6, 7, 9, 45-48).

Claim 28 depends from Claim 1, wherein B and the propyloxy substituents on Ar_2 are meta to each other (pp. 6, 7, 8, 9, 43-45).

Claim 29 depends from Claim 1, wherein B and the propyloxy substituents on Ar_2 are para to each other (pp. 6, 7).

Claim 30 depends from Claim 1, wherein B is selected from among the specified heteroaryl rings (pg. 7).

Claim 31 depends from Claim 30, wherein B is a tetrazole (pp. 7, 8).

Claim 32 depends from Claim 1, wherein B is $-(CH_2)_j$-$C(O)OR_4$ (pp. 4-5, 8, 9, 43-48).

Claim 33 depends from Claim 32, wherein R_4 is hydrogen (pp. 4-5, 8, 9, 43-48) or optionally substituted alkyl (pp. 4-5, 8, 12, 18-19).

Claim 34 depends from Claim 33, wherein said alkyl is a lower alkyl (pp. 8, 12).

Claim 35 depends from Claim 34, wherein said lower alkyl is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, and sec-butyl (pp. 8, 12).

Claim 36 depends from Claim 33, wherein R_4 is hydrogen (pp. 4-5, 8, 9, 43-48).

Claim 41 depends from any one of Claim 4 or Claim 5, wherein B is selected from among the specified heteroaryl rings (pg. 7).

Claim 42 depends from Claim 41, wherein B is a tetrazole (pg. 7).

Claim 43 depends from any one of Claim 4 or Claim 5, wherein B is $-(CH_2)_j$-$C(O)OR_4$ (pp. 4-5, 8, 9, 43-48).

Claim 44 depends from Claim 43, wherein R_4 is hydrogen (pp. 4-5, 8, 9, 43-48) or optionally substituted alkyl (pp. 4-5, 8, 12, 18-19).

Claim 45 depends from Claim 44, wherein said alkyl is a lower alkyl (pp. 8, 12).

Claim 46 depends from Claim 45, wherein said lower alkyl is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, and sec-butyl (pp. 8, 12).

Claim 47 depends from any one of Claim 4 or Claim 5, wherein R_4 is hydrogen (pp. 4-5, 8, 9, 43-48).

Claim 48 depends from Claim 4 wherein the compound is selected from the group of species shown (pp. 8, 43-45), or a pharmaceutically acceptable N-oxide, pharmaceutically acceptable prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, pharmaceutically acceptable ester, pharmaceutically acceptable amide, or pharmaceutically acceptable solvate thereof (please see support as recited in claim 1).

Claim 49 depends from Claim 5 wherein the compound is selected from the group of species shown (pp. 9, 45-48), or a pharmaceutically acceptable N-oxide, pharmaceutically acceptable prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, pharmaceutically acceptable ester, pharmaceutically acceptable amide, or pharmaceutically acceptable solvate thereof (please see support as recited in claim 1).

Independent claim 50 claims a compound having the structure of Formula III shown (pp. 9, 40-41).

Claim 51 depends from Claim 1, and claims a method of modulating a peroxisome proliferator-activated receptor (PPAR) function (pp. 9, 19-21) comprising contacting (pg. 20) said PPAR with a compound of claim 1 (pp. 3-5) and monitoring (pg. 21) a change in cell phenotype (pp. 20, 22-23), cell proliferation (pg. 20), activity of said PPAR (pg. 20), or binding of said PPAR (pp. 21-22) with a natural binding partner.

Claim 52 depends from Claim 51 wherein said PPAR is selected from the group consisting of PPARα, PPARδ, and PPARγ (pp. 1-3, 9, 19, 24-25).

Claims 53, 54, 55, 56, and 57 depend from Claims 1, 3 (as in claim 1 wherein Ar_2 is phenyl; pg. 5), 4 (as in claim 3 wherein the compound has the structure shown; pg. 5), 5 (as in claim 1 wherein Ar_2 is naphthyl; pg. 5), and 50 (wherein the compound is of Formulas III as shown; pg. 9), respectively, and each claim a method of inhibiting the formation of adipocytes (pp. 1-2, 10, 23) in a mammal comprising administering a therapeutically effective amount (pp. 10, 32) of a compound of Claims 1, 3, 4, 5, and 50, respectively, to the mammal.

Claims 59 depends from Claim 1, and claims a method of treating (pp. 32-34) a PPAR-modulated disease or condition (pp. 23-25) comprising identifying a patient in need thereof, and administering a therapeutically effective amount (pp. 10, 32) of a compound of Claim 1 to the patient (additionally, pg. 3).

Claims 60 depends from Claim 1, and claims a method of treating a metabolic disorder or condition (pp. 3, 10, comprising identifying a patient in need thereof, and administering a therapeutically effective amount (pp. 10, 32) of a compound of Claim 1 to the patient.

Claims 61 depends from Claim 1, and claims a method of treating a disease selected from the group consisting of obesity, diabetes, hyperinsulinemia, metabolic syndrome X, polycystic ovary syndrome, climacteric, disorders associated with oxidative stress, inflammatory response to tissue injury, pathogenesis of emphysema, ischemia-associated organ injury, doxorubicin-induced cardiac injury, drug-induced hepatotoxicity, atherosclerosis, and hypertoxic lung injury (collectively, pp. 10, 11, 23-25, 32-33) comprising identifying a patient in need thereof, and administering a therapeutically effective amount of a compound of Claim 1 to the patient.

Claim 62 depends from any one of Claims 59, 60, and 61, wherein the compound has the structure of Formula II (i.e., Ar_2 is phenyl).

Claim 63 depends from any one of Claims 59, 60, and 61, wherein the compound has the structure of Formula III.

Claim 64 depends from any one of Claims 59, 60, and 61, wherein the compound has the structure of Formula IV (i.e., Ar_1 is pyrimidine and Ar_2 is naphthyl).

Claims 61 depends from claim 1, and Claims a method of treating a PPAR-modulated disease or condition comprising identifying a patient in need thereof, and administering a therapeutically effective amount of the compound of Claim 50 to the patient.

Claims 66, 67, 68, 69 and 70 depend from Claims 1, 3, 4, 5, and 50, respectively, and claim a pharmaceutical composition comprising the compound of Claim 1, 3, 4, 5, or 50, and a pharmaceutically acceptable diluent, excipient, or carrier (pp. 26-31).

Grounds of rejection to be reviewed on appeal.

a. Whether claims 1-13, 18-36, 41-49, 51-56, 59-64, and 66-69 are unpatentable under 112 first paragraph for lack of enablement of prodrugs, metabolites, amides, esters, or solvates of compounds of Formula I.
b. Whether claims 51-57 and 59-64 are unpatentable under 112 first paragraph for lack of enablement of methods of modulation of PPAR and treatment of PPAR-mediated diseases.

Argument.

Claims 1-17, 19-36, 48-49, 51-53, 58-61, and 66-69, drawn to the preparation and/or use of pharmaceutically acceptable prodrugs, metabolites, esters, amides, and solvates of compounds of Formula I, are enabled under 35 U.S.C § 112.

For the following reasons, it is respectfully suggested that the specification is enabling with respect to the preparation of pharmaceutically acceptable prodrugs, metabolites, esters, amides, and solvates of compounds of Formula Iand it is requested that the rejection be withdrawn.

Esters and Amides

In explaining the rejection of prodrugs, metabolites, esters and amides as lacking enablement, it is stated that because the definitions of various substituent groups in Formula I encompasses free acids as well as esters and amides, it is not clear what other compounds of the invention to be are intended to be the claimed prodrugs, metabolites, esters and amides of compounds of Formula I. It is further noted that the specification does not disclose esters or amides capable of providing compounds of the invention.

With respect to this portion of the rejection under 35 USC 112, first paragraph, applicant believes that the examiner has stated an argument that the terms ester and amide (and prodrug and metabolite to the extent that such derivatives include esters and amides) are not enabled because it would not be clear to a person skilled in the art what compounds are being referred to. Applicant respectfully suggests that this is not the case. An ester can be formed from an alcohol or carboxylic acid. Likewise, an amide can be formed from an amine or carboxylic acid. As defined in claim 1, compounds of Formula I include carboxylic acids, alcohols, and amines, from which derivatives such as esters and amides can be formed using methods well known to persons skilled in the art. See Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999 (incorporated by reference in page 13 of the specification). Some of the compounds of Formula I which are carboxylic acids, alcohols, or amines also contain ester or amide functionalities. A person having skill in the art would recognize that such compounds could also be derivatized in the same manner as any other carboxylic acid, alcohol,

or amine to afford compounds that could be accurately and clearly described as esters or amides of the parent compounds.

Further clarification of the scope of the compounds that comprise esters and amides of the parent compounds of Formula I may be found in the specification, which defines the term "ester" on pages 14-15 and the term "amide" on page 13 in such a way to limit the scope of the variable groups introduced by derivitization of a compound of Formula I. Finally, with respect to the definition of B, which includes –(CH2)j-C(O)OR4, where R4 is H, alkyl, etc, applicant acknowledges that where B is –(CH2)j-C(O)OH, claim 1 encompasses only those esters of the B group carboxylate that also fall within the limitations of the definition of R4.

As for the reliance on the fact that specific examples of esters and amides are not disclosed in the specification, applicant believes that the 5th In re Wands factor, the presence or absence of working examples, has been overemphasized. 858 F.2d 731 (Fed. Cir. 1988). Here, the level of skill in the pharmaceutical arts is high, formation of esters and amides is a predictable area of the chemical arts, and the scope of the claims relating to esters and amides and the amount of experimentation necessary for their preparation is limited by the definition of "ester" and "amide" in the specification. Accordingly, applicant believes that an analysis of all the relevant In re Wands factors shows the rejected claims to be enabled with respect to esters and amides.

Prodrugs

The rejection of prodrugs as lacking enablement appears to be based on the following arguments: (1) that because prodrugs are defined in the specification to include esters and amides of compounds of Formula I, it is not clear whether compounds of Formula I which bear amide or ester moieties are excluded from being a potential pharmaceutically acceptable prodrug; (2) the specification does not provide any guidance as to where groups such as esters and amides should be placed on the structures of Formula I in order to give a prodrug; (3) in a clinical trial setting, it would require undue experimentation to determine whether a particular compound meets the criteria of a prodrug; and (4) the specification does not contain any working examples of prodrugs.

With respect to the first argument, while it is true that "prodrugs" of compounds of Formula I are defined by the specification to include esters and/or amides, the term "prodrug," encompasses a broader range of derivatives of compounds of Formula I than merely esters or amides. The examiner himself points this out, citing Bundgaard (Design of Prodrugs) for the proposition that prodrugs include polymer-bound prodrugs, acyclic precursors of heterocyclic compounds, conjugates of multiple drug molecules, and drugs bound to a carrier via a linker. Furthermore, applicant has never stated that all esters and amides of compounds of Formula I will function as prodrugs. Applicant believes that there is nothing indefinite about a claim that encompasses compounds that are within the scope of both a functional (prodrugs) and a structural (esters and amides) limitation, even though some of the same compounds may fall within the definition of both limitations.

The second argument, that the specification does not provide any guidance as to where groups such as esters and amides should be placed on the structures of Formula I in order to give a prodrug, gives too little credit to the abilities of a person having ordinary skill in the art. A skilled chemist who seeks to employ a given prodrug strategy, for example one disclosed in the Bundgaard reference cited by the examiner, to make a prodrug of a specific compound of Formula I can readily identify the available sites that can be modified to give a potential prodrug. This is because each prodrug strategy requires specific functional groups for its execution. For example, an amide prodrug would be obtained by derivatizing an amine or a carboxylic acid; an ester prodrug by derivatizing a hydroxyl group or a carboxylic acid; and an acyclic prodrug of a heterocyclic compound could only be employed when an appropriate heterocycle is present in the compound of Formula I. Thus, there is no need to disclose in the specification that which would be apparent to one having skill in the art. In re Wands 858 F.2d 731, 735 (Fed. Cir. 1988).

The third argument is that in a clinical trial setting it would require undue experimentation to determine whether a particular compound meets the criteria of a prodrug. Stated another way, applicant understands this argument to be that a person having ordinary skill in the art could not identify which derivatives of a compound of Formula I have utility as a prodrug without undue clinical experimentation, and therefore prodrugs are not enabled.

Applicant respectfully suggests that it has been improperly assumed that clinical trials are the proper context in which experimentation to determine whether a particular compound meets

the criteria of a prodrug occurs. The Federal Circuit has explained that "there is no per se requirement for clinical evidence to establish the utility of any invention." In re Cortwright, 165 F.3d 1353, 1355 (Fed. Cir. 1999). According to page 27 of the specification, a prodrug is "an agent that is converted into the parent drug in vivo." Clinical trials in humans are not required to determine whether in vivo conversion of a given prodrug to its parent drug occurs. Such a determination can be made through the use of in vivo pharmacokinetic studies in animals. Likewise, the efficacy of produgs can be determined through the use of disease models in animals. The Court of Customs and Patent Appeals has upheld the use of in vivo data to demonstrate utility where a person of ordinary skill in the art would reasonably believe that in vivo or even in vitro experimental results identify a pharmacological activity of a compound that is relevant to an asserted pharmacological use. Nelson v. Bowler, 626 F.2d 853 (C.C.P.A. 1980). Pharmacokinetic and efficacy studies in animals are a routine experimental step in the pharmaceutical arts. According to the Federal Circuit "a considerable amount of experimentation is permissible, if it is merely routine." In re Wands, 858 F.2d at 737. Applicant respectfully suggests that the type of experimentation needed to determine whether given derivatives of compounds of Formula I function as prodrugs is not undue.

The fourth and final argument is that the specification does not provide any working examples of prodrugs. According to the Court of Customs and Patent Appeals "[specific working] examples are not required to satisfy section 112, first paragraph." In re Strahilevitz, 668 F.2d 1229, 1232 (C.C.P.A. 1982). In Strahilevitz, the applicant did not disclose even a single operative embodiment. Id. at 1231. The court acknowledged that the claims at issue were extremely broad. Id. at 1232. Yet the court reversed the Board's holding of nonenablement, because the invention consisted in combining known prior art techniques. Id. at 1234. Likewise, the preparation of prodrugs involves the preparation of compounds of Formula I (which have been found enabled) combined with techniques to derivatize such compounds and analyze them for suitability as prodrugs, both of which techniques are known in the prior art. See, e.g., Bundgaard (Design of Prodrugs) and Hydrolysis in Drug and Prodrug Metabolism : Chemistry, Biochemistry, and Enzymology (Testa, Bernard and Mayer, Joachim M. Wiley-VHCA, Zurich, Switzerland 2003). Accordingly, applicant believes that specific working examples of prodrugs of compounds of Formula I are not required to satisfy 35 USC 112, first paragraph.

Metabolites

The Federal Circuit has defined a metabolite as "the compound formed in the patient's body upon ingestion of a pharmaceutical. The ingested pharmaceutical undergoes a chemical conversion in the digestion process to form a new metabolite compound." Schering Corp. v. Geneva Pharms., Inc., 339 F.3d 1373 (Fed. Cir. 2003). Accordingly, a person having ordinary skill in the art would recognize that pharmaceutically active metabolites compounds of Formula I can be made and used simply by administering compounds of Formula I to an animal or human subject. Furthermore, routine pharmacokinetic experimentation can be performed to identify relevant metabolites which can then be synthesized using methods known in the art and screened to determine if they are pharmaceutically active.

Solvates

The rejection of solvates of Formula I as lacking enablement is framed in terms of the factors identified by the Federal Circuit in In re Wands. 858 F.2d 731 (Fed. Cir. 1988). Briefly, those factors pertaining to enablement are 1) the nature of the invention, 2) the state of the prior art, 3) the predictability or unpredictability of the art, 4) the amount of direction or guidance presented, 5) the presence or absence of working examples, 6) the breadth of the claims, 7) the quantity of experimentation necessary, and 8) the level of skill in the art.

In support of the rejection, it is argued that because the art is unpredictable, there should be enabling disclosure in the specification in the form of working examples, and since there are no working examples, the specification lacks enablement with respect to solvates. However, The MPEP, Section 2164.02, states: "[t]he specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation." Furthermore, the Federal Circuit has stated that "[a] patent need not disclose what is well known in the art." In re Wands. 858 F.2d 731, 735 (Fed. Cir. 1988).

The experimentation required to identify solvates is well known in the art, and involves routine screening of various conditions under which solvates could form. See e.g., K.J. Guillory, Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids, in H.G. Brittain (ed.). Polymorphism in Pharmaceutical Solids, Vol. 95, (1999) pgs. 183-226. The Federal Circuit has

stated that "[e]nablement is not precluded by the necessity for some experimentation such as routine screening" and that even a large number of individual screening operations may be viewed as reasonable (and therefore not undue) by a person skilled in the art. In re Wands. 858 F.2d 731, 736-37, 740 (Fed. Cir. 1988). The fact that the art is unpredictable and that screening different conditions for solvate formation is a reliable method of identifying solvates indicates that a person having skill in the art would regard a large amount of such screening as a reasonable amount of experimentation. Furthermore, methods of performing such screening are well known in the art, and therefore there is no need to give detailed direction in the specification.

In further support of the rejection, it is argued that the specification discloses inoperative examples in that working examples of compounds of Formula I were prepared in the presence different solvents, including water, and that no solvates were formed. Applicant respectfully suggests that the nature of these working examples has been mischaracterized. With respect to formation of hydrates, the examples disclosed in the specification indicate that Na_2SO4, a drying agent, was used to remove trace amounts of water as part of the purification process following a number of the chemical steps involved in the syntheses of exemplary compounds. Thus, there is no evidence from the specification that water was present upon crystallization, or that water was in physical contact with solid compounds of Formula I, a precondition for the formation of a hydrate. Additionally, the examples disclosed in the specification also indicate that the purification process following a number of the chemical steps involved in the syntheses of exemplified compounds involved the removal of solvents. Thus, it is likely that even if solvates formed, they were decomposed during the process of solvent removal. Furthermore, the Federal Circuit has held that the presence of inoperative examples does not necessarily render claims invalid for lack of enablement. Atlas Powder Co. v. E.I. Du Pont De Nemours & Co., 750 F.2d 1569, 1576-77 (Fed. Cir. 1984). Finally, it is argued that the failure of the examples to show solvate formation indicates that there is no evidence that solvates of compounds of Formula I exist. A reference cited by the examiner indicates that "approximately one-third of [] pharmaceutically active substances are capable of forming crystalline hydrates." Vippagunta et al., Advanced Drug Delivery Reviews 48: 3-26 (2001). Applicant has suggested in response that the conditions used to synthesize the exemplified compounds were unfavorable for solvate

formation and therefore not indicative of the nonexistence of solvates. Combining the disclosure of the specification with the teachings of the prior art, however, claims to solvates are clearly enabled. Since the pending claims encompass a large number of individual compounds, and the claimed pharmaceutically acceptable solvates include solvents other than water, the prior art indicates that there is a substantial likelihood of success in forming solvates of at least some of the compounds of Formula I.

Claims 51-57 drawn to methods of modulation of PPAR and 59-64 drawn to treatment of PPAR-mediated diseases are enabled under 35 U.S.C § 112.

For the following reasons, it is respectfully suggested that the specification is enabling with respect to: a method of modulating a PPAR function; a method of inhibiting the formation of adipocytes in a mammal; a method of treating a PPAR-modulated disease or condition or a metabolic disorder generally; and a method of treating a disease selected from the group consisting of obesity, diabetes, hyperinsulinemia, metabolic syndrome X, polycystic ovary syndrome, climacteric, disorders associated with oxidative stress, inflammatory response to tissue injury, pathogenesis of emphysema, ischemia-associated organ injury, doxorubicin-induced cardiac injury, drug-induced hepatotoxicity, atherosclerosis, and hypertoxic lung injury; and it is requested that the rejection be withdrawn.

General Rejections of Claims 51-53, 57-61, and 65

Several general and specific arguments were made in support of the rejection of claims 51-53, 57-61, and 65 under 35 USC 112, first paragraph. Because it was not precisely specified which claims are being rejected for some of the reasons given, these arguments will be addressed first, followed by the arguments directed towards specific claims.

In support of the rejection, it is first argued that the specification does not enable one skilled in the art to use the claimed compounds as PPAR regulators. It is also claimed that no results in the PPAR binding activity assays disclosed on pages 21-22 are provided for any of the exemplified compounds. Applicant respectfully suggests that this is not the case. Exemplified

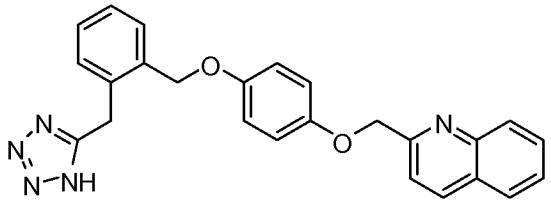
compounds were evaluated in a cell-based assay to determine their human PPAR activity, the results of which are disclosed on pages 48-51 of the specification.

It is further argued that the varying results obtained for the tested compounds indicate that the relevant area of receptor activity is highly structure specific and unpredictable. However, applicant respectfully points out that even if that is the case, applicant has disclosed assays and methods by which the claimed compounds can be routinely screened to evaluate their PPAR binding affinity. Because the PPAR binding activity can be determined through routine experimentation, a person having skill in the art has no need to be able to predict activity based on structure in order to practice the claimed invention.

It is also argued that there is no evidence on record which demonstrates that the *in-vitro* screening tests relied upon are recognized in the art as being predictive of success in the area of regulating PPAR. In support of this argument, examiner cites a PubMed abstract summarizing Fayer et al., J. Clin. Pharmacol. 41; 305 (2001), stating that factors other than plasma drug concentrations and potency of in vitro enzyme inhibition are important when extrapolating in vitro models of CYP inhibition to predict in vivo drug-drug interactions between RG 12525 (2-[[4-[[2-(1H-tetrazole-5-ylmethyl)phenyl]methoxy]phenoxy]methyl] quinolone), a novel PPAR-gamma agonist, and midazolam, a CYP3A4 substrate.

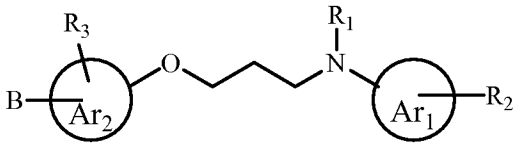
With respect to the Fayer reference, applicant notes that it is directed to an extrapolation of *in vitro* data predicting that administration of RG 12525 would have an effect on the metabolism of midazolam by CYP3A4 *in vivo*, and that no effect was found in the *in vivo* studies. Applicant respectfully suggests that the Fayer reference makes no claim about the predictive value or lack thereof of *in vitro* results in PPAR binding assays to *in vivo* PPAR modulating activity. PPAR-modulating activity and the ability of PPAR-modulators to effect specific biological results is the property at issue in the objected-to-claims. Therefore, the Fayer reference does not support the assertion that the art does not recognize *in-vitro* screening tests as being predictive of success in the area of regulating PPAR.

With respect to the Fayer reference, applicant further notes that RG 12525 is a distinct chemical entity from the claimed compounds. The structure of RG 12525 is as follows:



RG 12525

Compared to the claimed compounds of Formula I:



(I)

wherein Ar_1 is pyrimidine, it is clear that there are significant structural differences between RG 12525 and the claimed compounds. For example, RG 12525 does not possess the following structural features of the claimed compounds of Formula I: a tertiary amine, a pyrimidine ring system, an internal n-propylene group, etc. Likewise, the claimed compounds of Formula I do not possess the following structural features of RG 12525: a quinoline ring system, a –O-Ph-O- linker, etc. Since RG 12525 differs structurally from the claimed compounds, and pharmacokinetic and CYP inhibition properties are structure-dependent, it would be improper to infer that the claimed compounds would show an effect on the metabolism of midazolam by CYP3A4 using the *in vitro* methods of the Fayer reference, or that the such *in vitro* results would lack predictive value for the compounds of the claimed methods.

It is further argued that there is no evidence on record which demonstrates that *in vitro* PPAR binding assays such as those disclosed in the specification are recognized in the art as being reasonably predictive of success in any of the contemplated areas of regulating PPAR. Applicant respectfully suggests that this is not the case, and points to pages 1-3 and 23-25 of the specification, which cite numerous references correlating the regulation of PPAR with existing and potential treatments of numerous diseases. For example, correlations between *in vivo* efficacy and activity in PPAR binding assays for given compounds have been established - see

page 22 of the specification, citing *J. Biol. Chem.*, 1995, 270, 12953-6 for the proposition that an antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma.

For the reasons stated above, it is respectfully suggested that *in vitro* PPAR binding assays such as those disclosed in the specification are recognized in the art as being reasonably predictive of success in any of the contemplated areas of regulating PPAR and it is requested that the rejection be withdrawn.

A Method of Modulating a PPAR Function (Claims 51-52)

Claims 51-52, which recite "a method of modulating a PPAR function" were rejected because, it is argued, "the term 'modulating' generally encompasses blocking, activating, partial blocking and partial activating" and that none of the compounds were shown to have all these (revolutionary) properties. Applicant respectfully directs examiner's attention to the definition of the term "modulate" on pages 20-21 of the specification, which states:

> The term "modulate" refers to the ability of a compound of the invention to alter the function of a PPAR. A modulator may activate the activity of a PPAR, may activate or inhibit the activity of a PPAR depending on the concentration of the compound exposed to the PPAR, or may inhibit the activity of a PPAR. The term "modulate" also refers to altering the function of a PPAR by increasing or decreasing the probability that a complex forms between a PPAR and a natural binding partner. A modulator may increase the probability that such a complex forms between the PPAR and the natural binding partner, may increase or decrease the probability that a complex forms between the PPAR and the natural binding partner depending on the concentration of the compound exposed to the PPAR, and or may decrease the probability that a complex forms between the PPAR and the natural binding partner.

Applicant respectfully notes that nowhere in the specification is it suggested that any of the claimed compounds have the ability to block, activate, partially block and partially activate a PPAR function at the same time. According to the specification, modulation of PPAR function by a single compound at a given concentration may either activate or inhibit of a PPAR, or "increase[e] or decreas[e] the probability that a complex forms between a PPAR and a natural binding partner" The rejection appears to be based on a definition of the term "modulate" that is

at odds with the definition provided in the specification. The Federal Circuit has stated that "[c]laims must be read in view of the specification, of which they are a part." *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1314 (Fed. Cir. 2005). Therefore, applicant respectfully suggests that the examiner's proposed definition of the term "modulating" is not an appropriate basis for a rejection of claims 51-52 under 35 USC 112, first paragraph, and requests that the rejection be withdrawn.

It is further argued in the Office Action that "the specification did not provide any competent tests or data to establish that the compounds have the claimed 'calcium sensing receptor modulating activity.'" Applicant respectfully notes that since calcium sensing receptor modulating activity was not in fact claimed, the lack of such tests or data is not relevant to any of the claims currently pending.

Claims Rejected as "Reach-through" Claims (Claims 53, 57, 59-61, and 65)

Claims 53 and 57, which recite "a method of inhibiting the formation of adipocytes in a mammal," 59 and 65, which recite "a method of treating a PPAR-modulated disease," 60, which recites "a method of treating a metabolic disorder or condition," and 61, which recites "a method of treating a disease selected from the group consisting of obesity, diabetes, hyperinsulinemia, metabolic syndrome X, polycystic ovary syndrome, climacteric, disorders associated with oxidative stress, inflammatory response to tissue injury, pathogenesis of emphysema, ischemia-associated organ injury, doxorubicin-induced cardiac injury, drug-induced hepatotoxicity, atherosclerosis, and hypertoxic lung injury," were rejected because, it is argued, claims 53, 57, 59-61, and 65 are "reach through" claims. It is stated that "[r]each through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through to the corresponding therapeutic method of any or all diseases, disorders or conditions, for which they lack written description and enabling disclosure."

Applicant respectfully suggests that, in characterizing claims 53, 57, 59-61, and 65 as "reach through claims" claims 53, 57, 59-61, and 65 have not been read as a whole. Claim 53 reads: "A method of inhibiting the formation of adipocytes in a mammal comprising administering a therapeutically effective amount of a compound of Claim 1 to the mammal." Claim 57 reads: "A method of inhibiting the formation of adipocytes in a mammal comprising administering a therapeutically effective amount of a compound of Claim 50 to the mammal."

Claims 53 and 57 do not encompass a method of inhibiting the formation of adipocytes in general. Rather, they encompass a method by which the formation of adipocytes is inhibited by administering a therapeutically effective amount of a compound of Formula I (claim 1) or Formula III (claim 50). As currently pending, claim 59 reads: "A method of treating a PPAR-modulated disease or condition comprising identifying a patient in need thereof, and administering a therapeutically effective amount of a compound of Claim 1 to the patient." Claim 65 reads: "A method of treating a PPAR-modulated disease or condition comprising identifying a patient in need thereof, and administering a therapeutically effective amount of the compound of Claim 50 to the patient." Claims 59 and 65 do not encompass a method of treating a PPAR-modulated disease or condition in general. Rather, they encompass a method by which a PPAR-modulated disease or condition is treated by administering a therapeutically effective amount of a compound of Formula I (claim 1) or Formula III (claim 50). As currently pending, claim 60 reads: "A method of treating a metabolic disorder or condition comprising identifying a patient in need thereof, and administering a therapeutically effective amount of a compound of Claim 1 to the patient." Claim 60 does not encompass a method of treating a metabolic disorder or condition in general. Rather, it encompasses a method by which a metabolic disorder or condition is treated by administering a therapeutically effective amount of a compound of Formula I (claim 1). As currently pending, claim 61 reads: "A method of treating a disease ~~is~~ selected from the group consisting of obesity, diabetes, hyperinsulinemia, metabolic syndrome X, polycystic ovary syndrome, climacteric, disorders associated with oxidative stress, inflammatory response to tissue injury, pathogenesis of emphysema, ischemia-associated organ injury, doxorubicin-induced cardiac injury, drug-induced hepatotoxicity, atherosclerosis, and hypertoxic lung injury comprising identifying a patient in need thereof, and administering a therapeutically effective amount of a compound of Claim 1 to the patient." Claim 61 does not encompass a method of treating the listed diseases in general. Rather, it encompasses a method by which certain diseases are treated by administering a therapeutically effective amount of a compound of Formula I (claim 1).

Therefore, claims 53, 57, 59-61, and 65 are not "reach through claims" as examiner has defined that term. The fact that claims 53, 57, 59-61, and 65 are not "reach though claims" is further illustrated by comparison with the claims at issue in *Univ. of Rochester v. G.D. Searle &*

Co., 358 F.3d 916 (Fed. Cir. 2004). In *Univ. of Rochester*, the Federal Circuit rejected "reach through" claimed methods for inhibiting PGHS-2 activity in a human host comprising administering a compound, when the specification did not disclose the chemical structure of any such compound. *Id.* Here, the structures of the compounds to be administered are disclosed to be of Formula I (claims 53 and 59-61) and Formula III (claim 57 and 65). Applicant therefore suggests that the written description and enablement requirements under 35 USC 112, first paragraph have been met with respect to claims 53, 57, 59-61, and 65, and requests that the rejection be withdrawn.

Method of Treating a PPAR-Modulated Disease (Claims 59 and 65)

Claims 59 and 65, drawn to "a method of treating a PPAR-modulated disease or condition" were rejected as lacking enablement because they include disorders that are known to exist as well as those that may be discovered in the future, and, therefore, the claims are extremely broad. Applicant respectfully suggests that this is not the case. Although it is likely that diseases currently exist that are not known to be modulated by PPAR, it is respectfully suggested that a prima facie case has not been stated showing why that means that the claimed methods for their treatment are not enabled. Applicant notes that the no evidence has been cited in support of the assertion that a significant number of unknown PPAR-modulated diseases will be discovered in the future or why the treatment of such diseases are not enabled by the specification. As PPAR-mediated diseases are discovered, they can be treated by the method of claims 59 and 65. By way of example, at the time of filing, it was unknown that PPAR modulators could have an effect on Alzheimer's disease. PPARs had not yet been studied in the brain in great detail. Nevertheless, recent studies have yielded promising data. "In animal models of Alzheimer's disease, PPARgamma agonist treatment results in the reduction of amyloid plaque burden, reduced inflammation and reversal of disease-related behavioural impairment. In a recent phase II clinical trial, the use of the PPARgamma agonist rosiglitazone was associated with improved cognition and memory in patients with mild to moderate Alzheimer's disease." (Jiang Q et al., *CNS Drugs*, 2008;22(1):1-14.) The claims do not lack enablement because relevant diseases have not been identified by name. Applicant therefore requests that the rejection under 35 USC 112, first paragraph, be withdrawn.

In his enablement rejection of both the use of compounds as recited in the instant application for use in the treatment of PPAR-modulated diseases and for use in treatment of specifically-enumerated diseases below, the examiner states that although in vitro data is provided, there is "nothing in the specification how this data extrapolates to the treatment of all types of specific diseases [*sic*]." It is respectfully suggested that among those having skill in the art, such an extrapolation is unnecessary, since those teachings existed in the prior art at the time of filing. M.P.E.P. 2164.01 holds, "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.,* 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). One of skill in the art may easily select a compound from within the instant application and use the assay taught therein and/or routine methods well known in the art to test the compounds for efficacy in a particular disease or model thereof. This process as a whole is essentially drug development. No evidence that any undue experimentation would be necessary has been presented.

The art is replete with evidence of the utility of PPAR modulators in a diverse array of diseases, some of which were known at the time of filing and others of which were later elucidated. A search of the terms "PPAR metabolic disease" alone, in the PubMed online journal abstract database, yields over 2000 references. Among those references were review articles indicating the therapeutic potential of PPAR modulators in studies showing that "the ability of these nuclear receptors to integrate metabolic and inflammatory signalling makes them attractive targets for intervention in human metabolic diseases, such as atherosclerosis and type 2 diabetes, as well as for the modulation of inflammation and immune responses" (Bensinger SJ, and Tontonoz P, *Nature*, 2008 Jul 24;454(7203):470-7). References supporting the potential utility of PPAR modulation in ischemia/reperfusion (Tian-li Yue et al., Circulation. 2001 Nov 20;104(21):2588-94), oxidative stress and, by extension, hypertension, (Diep QN et al., *Hypertension*. 2002 Dec;40(6):866-71.) tissue injury and wound healing (Michalik L, Wahli W. *J Clin Invest.* 2006 Mar;116(3):598-606), neurologic injury (Deplanque D et al., *J Neurosci.* 2003 Jul 16;23(15):6264-71) and Alzheimer's disease, (Jiang Q et al., *CNS Drugs*, 2008;22(1):1-14), are easily found, among countless other diseases in which PPAR plays a role. These citations to support for PPAR-mediated diseases generally and individually indications are

provided by way of example. Recapitulation of the teachings of the prior art as it relates to each disease sought to be treated by the methods of the present invention is not a prerequisite for enablement: "A patent need not teach, and preferably omits, what is well known in the art." *Id.*, citing *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

A method of treating a disease selected from the group consisting of obesity, diabetes, hyperinsulinemia, metabolic syndrome X, polycystic ovary syndrome, climacteric, disorders associated with oxidative stress, inflammatory response to tissue injury, pathogenesis of emphysema, ischemia-associated organ injury, doxorubicin-induced cardiac injury, drug-induced hepatotoxicity, atherosclerosis, and hypertoxic lung injury (Claim 61)

Claim 61, drawn to "a method of treating a disease selected from the group consisting of obesity, diabetes, hyperinsulinemia, metabolic syndrome X, polycystic ovary syndrome, climacteric, disorders associated with oxidative stress, inflammatory response to tissue injury, pathogenesis of emphysema, ischemia-associated organ injury, doxorubicin-induced cardiac injury, drug-induced hepatotoxicity, atherosclerosis, and hypertoxic lung injury" was rejected as lacking enablement because, for example, "atherosclerosis is a common form of arteriosclerosis associated with the formation of artheromas which are deposits of yellow plaques containing cholesterol, lipids, and lipophages within the intima and inner media of arteries" and that "[t]his results in a narrowing of the arteries, which reduces the blood and oxygen flow to the heart and brain as well as to other parts of the body and can lead to a heart attack, stroke, or loss of function or gangrene of other tissues." It is not stated why the fact that atherosclerosis is a common form of arteriosclerosis, and that atherosclerosis results in the narrowing of the arteries, which can subsequently lead to heart attack, stroke, or loss of function or gangrene of other tissues means that claim 61 lacks enablement. Therefore, applicant respectfully suggests that examiner has failed to state a prima facie case of lack of enablement of claim 61 and it is requested that the rejection be withdrawn.

Finally, it is argued that the claims lack enablement because the specification discloses no correlation between the *in vitro* data provided and clinical efficacy. It is alleged that "[r]igorously planned and executed clinical trials . . . are required for selecting optimal dose and schedule for treatment of any particular disease." Molecular mode of action, pathology, and pharmacology are also cited as "required." These requirements, though clearly important prerequisites to drug approval for marketing and human consumption, are at odds with the direction of the courts as acknowledged in the MPEP itself regarding patentability. "[T]here is no per se requirement for clinical evidence to establish the utility of any invention." *In re Cortright*, 165 F.3d 1353, 1355 (Fed. Cir.), *reh'g denied*, 1999 U.S. App. LEXIS 9001 (1999). It is respectfully suggested that the examiner's reliance on lack of clinical proof of utility and safety is misplaced and irrelevant to the question of enablement.

For the reasons stated above, it is respectfully suggested that the specification is enabling with respect to the preparation of pharmaceutically acceptable prodrugs, metabolites, esters, amides, and solvates of compounds of Formula I; a method of modulating a PPAR function; a method of inhibiting the formation of adipocytes in a mammal; a method of treating a PPAR-modulated disease or condition or a metabolic disorder generally; and a method of treating a disease selected from the group consisting of obesity, diabetes, hyperinsulinemia, metabolic syndrome X, polycystic ovary syndrome, climacteric, disorders associated with oxidative stress, inflammatory response to tissue injury, pathogenesis of emphysema, ischemia-associated organ injury, doxorubicin-induced cardiac injury, drug-induced hepatotoxicity, atherosclerosis, and hypertoxic lung injury, and it is requested that the rejection be withdrawn.

Respectfully submitted,

October 27, 2008
Date

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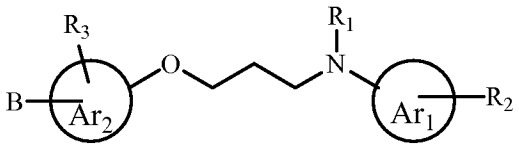
Claims appendix.

1. A compound having the structure of Formula I:

(I) 

wherein

Ar_1 is pyrimidine;

Ar_2 is selected from the group consisting of a monocyclic, a bicyclic, and a tricyclic carbocyclic aryl ring structure;

R_1 is selected from the group consisting of

alkyl, optionally substituted with a substituent selected from the group consisting of hydrogen, lower alkyl, optionally substituted carbocyclic or heterocyclic ring, halogen, perhaloalkyl, hydroxy, alkoxy, nitro, and amino; and

a five-membered or six-membered heteroaryl ring or a six-membered aryl ring, optionally substituted with one or more substituents selected from the group consisting of optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl; an alkoxy; cyano; nitro; an amino; an amido; perhaloalkyl; and halogen;

R_2 is selected from the group consisting of

hydrogen;

alkyl, optionally substituted with a substituent selected from the group consisting of hydrogen, lower alkyl, optionally substituted carbocyclic or heterocyclic ring, halogen, perhaloalkyl, hydroxy, alkoxy, nitro, and amino;

a five-membered or six-membered heteroaryl ring or a six-membered aryl ring, optionally substituted with one or more substituents selected from the group consisting of optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl; an alkoxy; halogen; and perhaloalkyl;

cyano; nitro; an amino; an amido; perhaloalkyl; and halogen;

R_3 is selected from the group consisting of hydrogen; alkyl, optionally substituted with a substituent selected from the group consisting of hydrogen, lower alkyl, optionally substituted carbocyclic or heterocyclic ring; hydroxy; halogen; amino; nitro; and cyano; and

B is a five-membered or six-membered heteroaryl ring, or $-(CH_2)_j$-$C(O)OR_4$, wherein j is 0 when Ar_2 is a bicyclic or tricyclic carbocyclic ring structure and j is 1 when Ar_2 is a monocyclic carbocyclic ring structure; and

R_4 is selected from the group consisting of

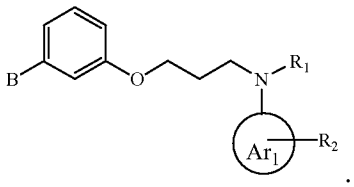
hydrogen;

alkyl, optionally substituted with a substituent selected from the group consisting of hydrogen, lower alkyl, optionally substituted carbocyclic or heterocyclic ring;

a five-membered or six-membered heteroaryl ring or a six-membered aryl ring, optionally substituted with one or more substituents selected from the group consisting of optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

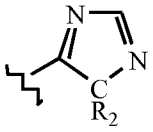
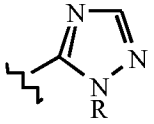
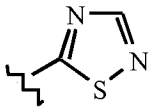
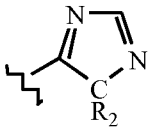
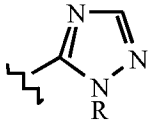
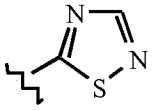
or a pharmaceutically acceptable N-oxide, pharmaceutically acceptable prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, pharmaceutically acceptable ester, pharmaceutically acceptable amide, or pharmaceutically acceptable solvate thereof.

2. The compound of Claim 1, wherein Ar_2 is selected from the group consisting of phenyl, naphthyl, anthracene, and phenanthrene.
3. The compound of Claim 2, wherein Ar_2 is phenyl.
4. The compound of Claim 3, having the structure:

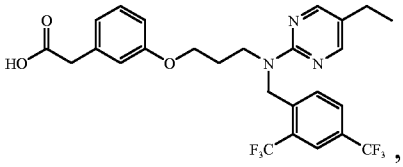
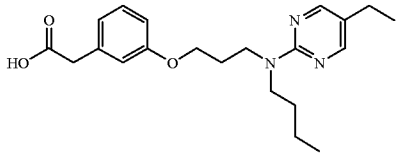


5. The compound of claim 2, wherein Ar_2 is naphthyl.
6. The compound of Claim 4 or Claim 5, wherein R_1 is alkyl, optionally substituted with one or more optionally substituted carbocyclic or heterocyclic rings.
7. The compound of Claim 6, wherein said alkyl is a lower alkyl.

8. The compound of Claim 7, wherein said lower alkyl is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, and sec-butyl.
9. The compound of Claim 6, wherein said carbocyclic ring is phenyl.
10. The compound of Claim 9, wherein said phenyl is optionally substituted with one or more substituents selected from the group consisting of lower alkyl, halogen, perhaloalkyl, hydroxy, alkoxy, nitro, and amino.
11. The compound of Claim 10, wherein said substituent is perhaloalkyl.
12. The compound of Claim 11, wherein said perhaloalkyl is trifluoromethyl.
13. The compound of Claim 1, wherein R_1 is alkyl substituted with 4-bis(trifluoromethyl)phenylmethyl.
14. (canceled)
15. (canceled)
16. (canceled)
17. (canceled)
18. The compound of any one of Claim 4 or Claim 5, wherein R_2 is optionally substituted alkyl.
19. The compound of Claim 18, wherein said alkyl is a lower alkyl.
20. The compound of Claim 19, wherein said lower alkyl is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, and sec-butyl.
21. The compound of Claim 20, wherein R_2 is ethyl.
22. The compound of Claim 1, wherein R_3 is hydrogen, halogen or optionally substituted alkyl.
23. The compound of Claim 22, wherein said optionally substituted alkyl is an optionally substituted lower alkyl.
24. The compound of Claim 23, wherein said optionally substituted lower alkyl is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, and sec-butyl.
25. The compound of Claim 1, wherein R_3 is methyl.
26. The compound of Claim 1, wherein R_3 is hydrogen.
27. The compound of Claim 1, wherein B and the propyloxy substituents on Ar_2 are ortho to each other.
28. The compound of Claim 1, wherein B and the propyloxy substituents on Ar_2 are meta to each other.

29. The compound of Claim 1, wherein B and the propyloxy substituents on Ar_2 are para to each other.
30. The compound of Claim 1, wherein B is a heteroaryl ring selected from the group consisting of furan, thiophene, pyrrole, pyrroline, pyrrolidine, oxazole, thiazole, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, isoxazole, isothiazole, triazole, tetrazole, thiadiazole, pyran, pyridine, piperidine, morpholine, thiomorpholine, pyridazine, pyrimidine, pyrazine, piperazine, triazine,  ,  , and  .
31. The compound of Claim 30, wherein B is a tetrazole.
32. The compound of Claim 1, wherein B is $-(CH_2)_j$-$C(O)OR_4$.
33. The compound of Claim 32, wherein R_4 is hydrogen or optionally substituted alkyl.
34. The compound of Claim 33, wherein said alkyl is a lower alkyl.
35. The compound of Claim 34, wherein said lower alkyl is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, and sec-butyl.
36. The compound of Claim 33, wherein R_4 is hydrogen.
37. (canceled)
38. (canceled)
39. (canceled)
40. (canceled)
41. The compound of any one of Claim 4 or Claim 5, wherein B is a heteroaryl ring selected from the group consisting of furan, thiophene, pyrrole, pyrroline, pyrrolidine, oxazole, thiazole, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, isoxazole, isothiazole, triazole, tetrazole, thiadiazole, pyran, pyridine, piperidine, morpholine, thiomorpholine, pyridazine, pyrimidine, pyrazine, piperazine, triazine,  ,  , and  .
42. The compound of Claim 41, wherein B is a tetrazole.

43. The compound of any one of Claim 4 or Claim 5, wherein B is $-(CH_2)_j-C(O)OR_4$.
44. The compound of Claim 43, wherein R_4 is hydrogen or optionally substituted alkyl.
45. The compound of Claim 44, wherein said alkyl is a lower alkyl.
46. The compound of Claim 45, wherein said lower alkyl is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, and sec-butyl.
47. The compound of any one of Claim 4 or Claim 5, wherein R_4 is hydrogen.
48. The compound of Claim 4 selected from the group consisting of:


, and

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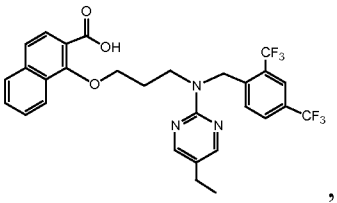
or a pharmaceutically acceptable N-oxide, pharmaceutically acceptable prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, pharmaceutically acceptable ester, pharmaceutically acceptable amide, or pharmaceutically acceptable solvate thereof.

49. The compound of Claim 5 selected from the group consisting of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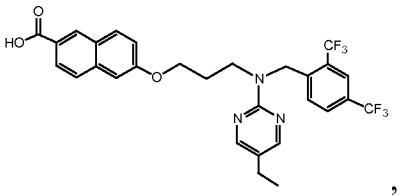
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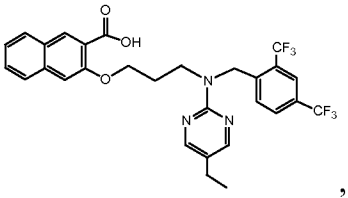
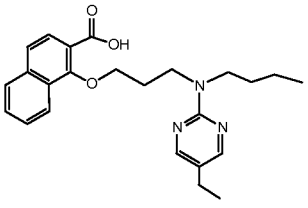
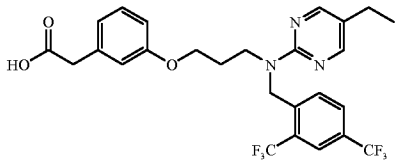

, and

,

or a pharmaceutically acceptable N-oxide, pharmaceutically acceptable prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, pharmaceutically acceptable ester, pharmaceutically acceptable amide, or pharmaceutically acceptable solvate thereof.

50. A compound having the structure of Formula III:

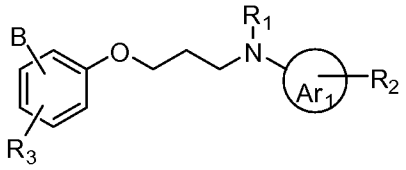


(III).

51. A method of modulating a peroxisome proliferator-activated receptor (PPAR) function comprising contacting said PPAR with a compound of Claim 1 and monitoring a change in cell phenotype, cell proliferation, activity of said PPAR, or binding of said PPAR with a natural binding partner.
52. The method of Claim 51, wherein said PPAR is selected from the group consisting of PPARα, PPARδ, and PPARγ.
53. A method of inhibiting the formation of adipocytes in a mammal comprising administering a therapeutically effective amount of a compound of Claim 1 to the mammal.
54. A method of inhibiting the formation of adipocytes in a mammal comprising administering a therapeutically effective amount of a compound of Claim 3 to the mammal.
55. A method of inhibiting the formation of adipocytes in a mammal comprising administering a therapeutically effective amount of a compound of Claim 4 to the mammal.
56. A method of inhibiting the formation of adipocytes in a mammal comprising administering a therapeutically effective amount of a compound of Claim 5 to the mammal.
57. A method of inhibiting the formation of adipocytes in a mammal comprising administering a therapeutically effective amount of a compound of Claim 50 to the mammal.
58. (cancelled)
59. A method of treating a PPAR-modulated disease or condition comprising identifying a patient in need thereof, and administering a therapeutically effective amount of a compound of Claim 1 to the patient.
60. A method of treating a metabolic disorder or condition comprising identifying a patient in need thereof, and administering a therapeutically effective amount of a compound of Claim 1 to the patient.
61. A method of treating a disease ~~is~~ selected from the group consisting of obesity, diabetes, hyperinsulinemia, metabolic syndrome X, polycystic ovary syndrome, climacteric, disorders associated with oxidative stress, inflammatory response to tissue injury, pathogenesis of

emphysema, ischemia-associated organ injury, doxorubicin-induced cardiac injury, drug-induced hepatotoxicity, atherosclerosis, and hypertoxic lung injury comprising identifying a patient in need thereof, and administering a therapeutically effective amount of a compound of Claim 1 to the patient.

62. The method of any one of Claims 59, 60, or 61, comprising administering a therapeutically effective amount of a compound having the structure of Formula II to said patient:



II

wherein

Ar_1 is pyrimidine;

R_1 is selected from the group consisting of

alkyl, optionally substituted with a substituent selected from the group consisting of hydrogen, lower alkyl, optionally substituted carbocyclic or heterocyclic ring, halogen, perhaloalkyl, hydroxy, alkoxy, nitro, and amino;

a five-membered or six-membered heteroaryl ring or a six-membered aryl ring, optionally substituted with one or more substituents selected from the group consisting of optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl; an alkoxy; cyano; nitro; an amino; an amido; perhaloalkyl; and halogen;

R_2 is selected from the group consisting of

hydrogen;

alkyl, optionally substituted with a substituent selected from the group consisting of hydrogen, lower alkyl, optionally substituted carbocyclic or heterocyclic ring, halogen, perhaloalkyl, hydroxy, alkoxy, nitro, and amino;

a five-membered or six-membered heteroaryl ring or a six-membered aryl ring, optionally substituted with one or more substituents selected from the group consisting of optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl; an alkoxy; halogen; and perhaloalkyl;

cyano; nitro; an amino; an amido; perhaloalkyl; and halogen;

R_3 is selected from the group consisting of hydrogen; alkyl, optionally substituted with a substituent selected from the group consisting of hydrogen, lower alkyl, optionally substituted carbocyclic or heterocyclic ring; hydroxy; halogen; amino; nitro; and cyano; and

B is a five-membered or six-membered heteroaryl ring, or $–CH_2\text{-}C(O)OR_4$; and

R_4 is selected from the group consisting of

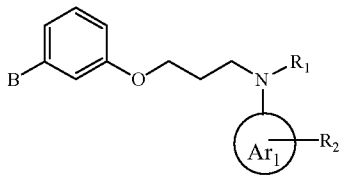
hydrogen;

alkyl, optionally substituted with a substituent selected from the group consisting of hydrogen, lower alkyl, optionally substituted carbocyclic or heterocyclic ring;

a five-membered or six-membered heteroaryl ring or a six-membered aryl ring, optionally substituted with one or more substituents selected from the group consisting of optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

or a pharmaceutically acceptable N-oxide, pharmaceutically acceptable prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, pharmaceutically acceptable ester, pharmaceutically acceptable amide, or pharmaceutically acceptable solvate thereof.

63. The method of any one of Claims 59, 60, or 61, comprising administering a therapeutically effective amount of a compound having the structure of Formula III to said patient:



III

wherein

Ar_1 is pyrimidine;

R_1 is selected from the group consisting of

alkyl, optionally substituted with a substituent selected from the group consisting of hydrogen, lower alkyl, optionally substituted carbocyclic or heterocyclic ring, halogen, perhaloalkyl, hydroxy, alkoxy, nitro, and amino;

a five-membered or six-membered heteroaryl ring or a six-membered aryl ring, optionally substituted with one or more substituents selected from the group consisting of optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl; an alkoxy; cyano; nitro; an amino; an amido; perhaloalkyl; and halogen;

R_2 is selected from the group consisting of

hydrogen;

alkyl, optionally substituted with a substituent selected from the group consisting of hydrogen, lower alkyl, optionally substituted carbocyclic or heterocyclic ring, halogen, perhaloalkyl, hydroxy, alkoxy, nitro, and amino;

a five-membered or six-membered heteroaryl ring or a six-membered aryl ring, optionally substituted with one or more substituents selected from the group consisting of optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl; an alkoxy; halogen; and perhaloalkyl;

cyano; nitro; an amino; an amido; perhaloalkyl; and halogen;

B is a five-membered or six-membered heteroaryl ring, or $–CH_2$-$C(O)OR_4$; and

R_4 is selected from the group consisting of

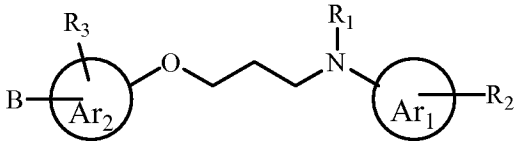
hydrogen;

alkyl, optionally substituted with a substituent selected from the group consisting of hydrogen, lower alkyl, optionally substituted carbocyclic or heterocyclic ring;

a five-membered or six-membered heteroaryl ring or a six-membered aryl ring, optionally substituted with one or more substituents selected from the group consisting of optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

or a pharmaceutically acceptable N-oxide, pharmaceutically acceptable prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, pharmaceutically acceptable ester, pharmaceutically acceptable amide, or pharmaceutically acceptable solvate thereof.

64. The method of any one of Claims 59, 60, or 61, comprising administering a therapeutically effective amount of a compound having the structure of Formula IV to said patient:



IV

wherein

Ar_1 is pyrimidine;

Ar_2 is napthyl

R_1 is selected from the group consisting of

alkyl, optionally substituted with a substituent selected from the group consisting of hydrogen, lower alkyl, optionally substituted carbocyclic or heterocyclic ring, halogen, perhaloalkyl, hydroxy, alkoxy, nitro, and amino;

a five-membered or six-membered heteroaryl ring or a six-membered aryl ring, optionally substituted with one or more substituents selected from the group consisting of optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl; an alkoxy; cyano; nitro; an amino; an amido; perhaloalkyl; and halogen;

R_2 is selected from the group consisting of

hydrogen;

alkyl, optionally substituted with a substituent selected from the group consisting of hydrogen, lower alkyl, optionally substituted carbocyclic or heterocyclic ring, halogen, perhaloalkyl, hydroxy, alkoxy, nitro, and amino;

a five-membered or six-membered heteroaryl ring or a six-membered aryl ring, optionally substituted with one or more substituents selected from the group consisting of optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl; an alkoxy; halogen; and perhaloalkyl;

cyano; nitro; an amino; an amido; perhaloalkyl; and halogen;

R_3 is selected from the group consisting of hydrogen; alkyl, optionally substituted with a substituent selected from the group consisting of hydrogen, lower alkyl, optionally substituted carbocyclic or heterocyclic ring; hydroxy; halogen; amino; nitro; and cyano; and

B is a five-membered or six-membered heteroaryl ring, or $-(CH_2)_j$-$C(O)OR_4$, wherein j is 0 or 1; and

R_4 is selected from the group consisting of

hydrogen;

alkyl, optionally substituted with a substituent selected from the group consisting of hydrogen, lower alkyl, optionally substituted carbocyclic or heterocyclic ring;

a five-membered or six-membered heteroaryl ring or a six-membered aryl ring, optionally substituted with one or more substituents selected from the group consisting of

optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

or a pharmaceutically acceptable N-oxide, pharmaceutically acceptable prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, pharmaceutically acceptable ester, pharmaceutically acceptable amide, or pharmaceutically acceptable solvate thereof.

65. A method of treating a PPAR-modulated disease or condition comprising identifying a patient in need thereof, and administering a therapeutically effective amount of the compound of Claim 50 to the patient.
66. A pharmaceutical composition comprising a compound of Claim 1 and a pharmaceutically acceptable diluent, excipient, or carrier.
67. A pharmaceutical composition comprising a compound of Claim 3 and a pharmaceutically acceptable diluent, excipient, or carrier.
68. A pharmaceutical composition comprising a compound of Claim 4 and a pharmaceutically acceptable diluent, excipient, or carrier.
69. A pharmaceutical composition comprising a compound of Claim 5 and a pharmaceutically acceptable diluent, excipient, or carrier.
70. A pharmaceutical composition comprising the compound of Claim 50 and a pharmaceutically acceptable diluent, excipient, or carrier.

Evidence appendix

(None)

Related proceedings appendix.

Not applicable.